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10/552,881	07/17/2006	Simone Charlotte Vonwiller	ALAR8.001 APC	9163

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
12/11/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/552,881	VONWILLER ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-69* is/are pending in the application.

4a) Of the above claim(s) *51-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-50 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Applicants' amendments and remarks regarding the Request for Continued Examination (RCE) of Application N° 10/552,881, filed 22 September 2009, are acknowledged and entered on the record. The Examiner acknowledges the following:

No claims have been added or cancelled.

Claims 36 and 69 have been amended. Claim 69 is amended to change the dependency from claim 36 to claim 38. The amendments to claim 36 add the functional limitations that the method produces a "gel having a single type of cross-linkage" and that "the cross-linked polysaccharide gel is sufficiently cross-linked to resist degradation". Support for the former limitation is alleged in the specification. Support for the latter limitation is found where indicated by Applicants. The former amended limitation is discussed herein below (see **NEW REJECTIONS**).

Thus, claims 36-50 and 67-69 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 22 April 2009:

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-41, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao (WO 00/46253).

The instant claims are directed to a process for producing a cross-linked gel comprising mixing (e.g. contacting) an alkaline-based polysaccharide medium with an epoxide cross-linking agent via ether bonds, drying said gel without removing the ether bonds, washing the gel with a water miscible solvent and neutralizing said gel using an acidic medium (claim 1). The polysaccharide is further recited as hyaluronic acid or (HA) (claims 37-39). The epoxide is further recited as butanediol diglycidyl ether (claims 40 and 41). The mixing, drying and washing steps are recited as being performed under alkaline conditions with acetone (claims 46 and 47).

Zhao teaches a method for producing a cross-linked gel wherein an alkaline solution of hyaluronic acid in sodium hydroxide is mixed with varied volumes of the multifunctional epoxide 1,2,7,8,-diepoxyoctane, drying said mixture into a gel formation, purifying (e.g. washing) the dried gel using acetone/water, acetone and isopropyl alcohol (IPA), and neutralizing said gel in an acidic medium of acetone/hydrochloric acid at pH 5 (Example 6 and claim 1). Claim 4 teaches additional cross-linking agents such as butanediol diglycidyl ether.

PREVIOUS RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-41, 46 and 47, under 35 USC 102(b) as being anticipated by Zhao et al. (WO 00/46253), have been fully considered, but are not persuasive.

Applicants allege that Zhao teaches away from the method recited in the instant claim 36, particularly since Zhao teaches that the hyaluronic acid (HA)/epoxide mixture is allowed to sit for a period of 24 hours prior to the drying step, which occurs over an additional 48 hours. Applicants further allege that Zhao teaches away from the instantly claimed invention on the grounds that Zhao teaches the formation of *multiple types* of cross-linkages, whereas the instant claims are directed to the formation of a single type of *cross-linkage* [*emphases added*].

In response to Applicants' argument that the references fail to show certain features of the instantly claimed invention, it is noted that the features upon which Applicants rely (i.e., 72-hour period from mix to dry; single versus multiple cross-linkage formation) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thus, for these reasons, Applicants' arguments are found unpersuasive. The above rejection is hereby maintained. The above rejection is hereby maintained as well as extended to new claims 67-69.

RESPONSE TO NEW ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-41, 46, 47 and 67-69 under 35 USC 102(b) as being anticipated by Zhao, has been fully considered, but is not persuasive.

Applicants argue that the amendments made to claim 36 concerning the addition of the aforementioned functional limitations is sufficient enough to overcome the maintained anticipation rejection. Applicants further provide further argument that the Zhao reference departs from the instantly claimed composition on the grounds that Zhao discloses a process from forming HA gels having multiple (i.e. two or more types of) cross-linkages as opposed to gels having a single type of cross-linkage, as instantly claimed.

In response, the Examiner respectfully submits that Applicants' amendments and remarks are directed to a purported physical property of the composition prepared using the instantly claimed method. Applicants have presented no amendments or arguments concerning the method or materials used by the reference. As such, the Examiner continues to interpret the reference as reading on the instantly claimed invention for the reasons already made of record. Furthermore, "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." (see MPEP §2112.01(I)). Since the teachings of Zhao employ the instantly claimed method, using the instantly claimed components, it follows, absent a clear showing of evidence to the contrary, that the invention of Zhao results in the instantly claimed composition.

Thus, for these reasons, Applicants' arguments are found unpersuasive. The above rejection is hereby **maintained**.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 36-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao (WO 00/46253) in view of Mälson (WO 87/07898).

The instant claims are directed to a process for producing a cross-linked hyaluronic gel, as discussed above. Various conditions under which the procedure is performed such as pH (claim 42), component concentration (claim 43), and reaction and drying temperatures (claims 44 and 45) are recited. Claims 48 and 49 recite step (d.) as further comprising freeze-drying or lyophilizing the produced gel and reconstituting it in phosphate buffered saline (PBS). The term "reconstituting", viewed in its broadest and most reasonable terms, is interpreted by the Examiner as reciting "restoration to a former condition by adding water". In the case of claim 49, this is interpreted as restoration using a water-based medium such as PBS. Claim 50 recites the gel as further comprising a biologically active substance.

The teachings to Zhao are discussed above. Zhao further teaches that the starting solution for an alkaline solution is preferably at a pH of 10 or more and that the reaction may effected at a temperature in the range of 15 to 50°C (pg. 9, line 27 to pg. 10, line 4). Example 6 further teaches that the starting solution is a 2.5% solution of hyaluronic acid in sodium hydroxide (HA/NaOH) which is mixed with varying amounts of epoxide. Tables 1-3 teach varying "feeding ratios" of HA to the cross-linking compound. Drying of the gel at a temperature of at least about 35°C (i.e. in a 37°C oven) is taught (Examples 1-3). Restoration of the gel product from a dried film or sheet format by immersing it in PBS is taught (pg. 11, lines 11-15). Incorporation of a biologically active substance into the gel is taught (claims 1, 15, 22 and 23).

Freeze drying as a means for drying the gel to a film or sheet format is not expressly taught by Zhao. Nor is it expressly taught that the gel is dried under a vacuum.

Mälson teaches the preparation of a cross-linked polymerized gel product (e.g. an insoluble, porous spongy material) wherein sodium hyaluronate or hyaluronic acid is dissolved into sodium hydroxide, mixed with 0.15 wt./volume % butanediol diglycidyl ether (BDDE), washed (e.g. dialysed) with water and then dried to form the film under acidic conditions (Example 1 and claims 1-7). Example 9 expressly teaches drying the formulation using freeze-drying. Example 19 teaches incorporation of Vitamin A as a biologically active substance which is controllably released from said gel by immersion into a volume of buffer. "Physiological saline" such as PBS is taught as being used to swell or restore the gels (pg. 9, second paragraph; pg. 8, bottom paragraph).

Mälson does not expressly teach the steps of the method in order or all of the specific reaction conditions as instantly claimed (e.g. vacuum drying).

In view of the combined teachings of the prior art, one of ordinary skill in the art, at the time of the invention, would have been motivated to use the instantly claimed method in order to prepare a hyaluronic acid and epoxide cross-linked polymerized gel. Such would have been obvious in the absence of evidence to the contrary since Zhao expressly teaches the procedure with the exception of certain particular claimed parameters (i.e. compositional epoxide percentage, vacuum drying, or freeze-drying). With the exception of certain adjustable parameters, the art taught by Mälson overlaps in its teaching of method steps (e.g. alkaline starting solutions mixed with epoxides) and components (e.g. hyaluronic acid and butanediol diglycidyl ether) with Zhao, both of which can be incorporated to arrive at the instant method claims. Lyophilization, while not taught by Zhao, is a method which is well known in the art by the skilled artisan as a means for preserving gels as dehydrated films. Furthermore, though neither of the practiced inventions expressly teaches using a drying the gel preparations at higher temperatures using a vacuum drying oven, one of ordinary skill in the art would be well motivated to employ such an oven if for no other reason than to minimize the risk of particulate contamination in the dried gel product.

Therefore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the gel-producing method practiced by Zhao with the freeze-drying gel preparation step taught by Mälson since the combined teachings disclose the instantly claimed method for producing a biologically active cross-linked gel composition. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

While neither Zhao nor Mälson teach the instantly claimed pH, temperature and percentage ranges, as instantly claimed by Applicants, Zhao offers a broader teaching of said parameters in the practiced Examples and Tables, as discussed above. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. As evidenced by the combination of the two teachings, it would have been customary for an artisan of ordinary skill, for example, to adjust the amount of multifunctional epoxide-based cross-linking agent, in order to achieve the desired gel composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

PREVIOUS RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-50 under 35 USC 103(a) over the combined teachings of Zhao et al. and Mälson et al. have been fully considered but they are not persuasive.

Applicants allege that the combined teachings provided by the references teach away from the instantly claimed invention on the grounds of the types/quantity of cross-linkages formed by Zhao (e.g. single versus multiple), as discussed above. Applicants further discuss that the teachings of Mälson describe a cross-linking process in which *excess cross-linker is removed prior to drying*, which is thus allegedly contrasted to the instantly claimed limitation whereby *drying*

takes place without substantially removing epoxide [*emphases added*]. Applicants further attest to the presence of excess cross-linker being present during the drying step.

In response to Applicants' argument that the references fail to show certain features of the instantly claimed invention, it is noted that the features upon which Applicants rely (i.e., single versus multiple cross-linkage formation; presence of excess cross-linker during any step) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the Examiner respectfully disagrees with Applicants' remarks regarding the presence excess cross-linker. The instantly claimed method step (b.) recites that substantially no epoxide is removed from the gel prep during the drying step. Claim 1 of Mälson recites that the reagents are mixed, that the excess bi- or polyfunctional reagent (e.g. the epoxide cross-linker) is removed and then in a second step, the gel prep is dried. Thus Mälson does not teach or suggest the removal of the epoxide cross-linker during the drying step, but rather prior to the drying step. As such, the removal of excess cross-linker as taught by Mälson, though not a limitation of the rejected claims, does read on the instantly claimed method.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore maintained. The above rejection is hereby maintained as well as extended to new claims 67-69.

NEW RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 36-50 and 67-69 under 35 USC 103(a) as being unpatentable over the combined teachings of Zhao et al. and Mälson et al. have been fully considered but they are not persuasive.

Applicants allege that the cross-linking "advantages" conferred by the process disclosed by Zhao relate only to HA having multiple types of cross-linkages. Applicants also refer to a passage within the Zhao reference which discusses the density of and degree to which cross-linking occurs within the products produced by Zhao.

Regarding these remarks, the Examiner respectfully maintains that the reference continues to read upon the instantly claimed invention for the reasons already discussed above (see **RESPONSE TO NEW ARGUMENTS**, above). Furthermore, the passage is interpreted as disclosing a "single type of" cross-linkage formed from the method, namely the formation of a double cross-link. This type of cross-link, which is established using the same materials and methods, is also taught as providing increased biostability against gel degradation.

DECLARATION UNDER 37 CFR §1.132

The Declaration under 37 CFR 1.132 filed 22 September 2009, is acknowledged and has been reviewed, but is insufficient as evidence in overcoming the rejection of the instant claims based upon the combined teachings of Zhao and Mälson as set forth in the last Office Action. It appears that Applicants compare the instant composition to two different commercially produced formulations (e.g. Perlane™ and Restylane™) in Example 1 of the instant disclosure. Further experimentation is provided where three formulations (e.g. Juvederm™ is tested instead of

Perlane™) are subjected hyaluronidase assays in order to demonstrate, compare and contrast their abilities to withstand degradation. Review of the experimental method and data provided by Applicants is considered as not being commensurate in scope with the arguments of record. Namely, the affidavit neither compares nor distinguishes the instantly claimed compositions from those which are produced by the art of record. Rather Applicants merely re-emphasize how the instant invention distinguishes over that which is already commercially known and/or reiterate that which is already on record in the specification. Furthermore, it is not clear how, if at all, any of the trademarked products of the specification and affidavit relate to those compositions which are produced by the combined teachings Zhao and Mälson. That being said, it is not clear what evidence the experiments of the affidavit contribute to overcoming the rejections of record.

As such, the Declaration, while having been fully considered, is **not persuasive**.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

NEW REJECTIONS

In light of Applicants' amendments to claim 36, the following rejection has been newly added:

CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Independent claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claim 36, as presently amended, recites a functional limitation whereby the cross-linked polysaccharide gel produced has "*a single type of cross-linkage*" [*emphasis added*]. Applicants' response, dated 22 September 2009, alleges support for the amendments made to claim 1. However, while the passages disclosed by Applicants do provide support for the amendment concerning resistance to degradation, they provide *no* discussion which could be construed as conveying support for the amended "single type of cross-linkage" limitation. Thus, the addition of the aforementioned limitation constitutes **new matter**, since Applicants' disclosure seemingly lacks support for the added limitation. Herein, and for the purposes of continued examination on the record, the amended functional limitation is interpreted by the Examiner as reciting that the composition produced can have a given type of cross-linkage (e.g. double cross-link) which occurs as a result of achieving the method.

The remaining dependent claims 37-50 and 67-69 are rejected since they depend from the rejected base claim 36.

All claims have been rejected; no claims are allowed.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner

should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615